The avian hippocampal formation and the stress response

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ABSTRACT

Though widely studied for its function in memory and navigation, the hippocampal formation in mammals also plays an important role in regulating the stress response. If this is an ancestral feature of the hippocampus, then it is likely that the avian hippocampal formation (HF) plays a similar role. Indeed, the avian HF strongly expresses both mineralocorticoid and glucocorticoid receptors, and has indirect projections to the paraventricular nucleus of the hypothalamus, which controls the hypothalamic-pituitary-adrenal (HPA) axis. Hippocampal lesions increase HPA activity, while electrical stimulation suppresses it. In addition, adult hippocampal neurogenesis in birds is reduced in response to different acute and chronic stressors, as it is in mammals. Because the mammalian hippocampus is functionally specialized along its septo-temporal axis, with the temporal pole playing a more important role in the stress response, the hypothesis is put forward that a similar functional specialization exists in birds along the rostro-caudal hippocampal axis. Some, though not all, of the evidence supports a rostro-caudal functional gradient. The evidence for whether this is equivalent to the mammalian septo-temporal organization is currently ambiguous at best, and needs to be more extensively investigated.

Thanks to the seminal studies on patient HM, the hippocampus is indelibly connected with learning and memory [Scoville and Milner, 1957]. In the bird literature as well, the hippocampal formation (HF) has been connected with memory and with spatial navigation [Bingman et al., 1985, Bingman et al., 1988, Krebs et al., 1989, Sherry and Vaccarino, 1989, see also several contributions to this issue]. However, it is well known that the mammalian hippocampus has other functions than memory processing, most importantly in regulating the stress response and emotions [Bannerman et al., 1999, Mcewen et al., 1994]. When looking for homologies, similarities and differences between the mammalian and avian HF, it is important that we also explore these other functions of the mammalian hippocampus, and ascertain whether they are present in birds as well.

Role of the mammalian hippocampus in the stress response

One function of the mammalian hippocampus is to serve as part of the negative feedback loop that controls the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis [Jacobson and Sapolsky, 1991]. The hippocampus has the highest density of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) anywhere in the mammalian brain, and is one of the few brain areas to express both receptor types. This indicates that the mammalian hippocampus is a target organ for glucocorticoid hormones such as corticosterone and cortisol (henceforth abbreviated to CORT). Because MR has a high affinity for CORT, it responds to baseline levels of these hormones, while the lower CORT affinity of GR cause it only to respond to higher, stress-induced CORT levels. Evidence from stimulation and lesion studies suggests that the hippocampus is especially involved in reducing circulating CORT after stimulation by a stressor, and is responsible for the troughs of the circadian rhythm (CORT is highest at waking up, lowest at the end of the active period) [Jacobson and Sapolsky, 1991]. The role of the mammalian hippocampus in controlling HPA axis activity seems to be restricted to HPA activation caused by “anticipatory” or psychogenic stressors, like social stressors or predator attack, but does not regulate HPA activation that is caused by homeostatic mechanisms, like changes in blood glucose levels [Herman and Mueller, 2006].

Different subdivisions of the mammalian hippocampus seem to be involved in the different influences of the hippocampus on the HPA axis. Lesions of the temporal pole (ventral hippocampus in rodents) do not affect the circadian CORT rhythm, but do affect the recovery from a psychogenic HPA axis activation [Herman and Mueller, 2006]. This suggests that the septal pole (dorsal hippocampus in rodents), in addition to playing an important role in cognitive functions [Fanselow and Dong, 2010], is also important in regulating the circadian rhythm in CORT production. The function of the temporal hippocampus in controlling the recovery from a psychogenic stressor is mediated mainly by the temporal subiculum, which sends excitatory (glutamatergic) projections to a number of regions with inhibitory influence on the paraventricular nucleus (PVN; the hypothalamic region at the top of the HPA axis), including the Bed Nucleus of the Stria Terminalis (BNST), the peri- and sub-paraventricular hypothalamus, the ventrolateral preoptic area (vlPOA) of the hypothalamus, and the ventrolateral dorsomedial hypothalamus (vlDMH) [Fig. 1A; Herman and Mueller, 2006, O'Mara, 2005, Ulrich-Lai and Herman, 2009]. The BNST in particular has been argued to be the most important of these relay stations [Radley, 2012]. Lesions of the temporal (but not the septal) hippocampus also have an anxiolytic effect [McHugh et al., 2004], although it depends on how anxiety is measured [Degroot and Treit, 2004].

One process that seems especially sensitive to the effects of chronic stress is adult hippocampal neurogenesis (AHN), the process of the addition or turnover of new neurons throughout life. In the mammalian hippocampus, this happens exclusively to the granule cells of the dentate gyrus (DG) [Altman, 1962, Altman and Das, 1965a, Altman and Das, 1965b]. Chronic negative stress (e.g. chronic restraint stress) down-regulates the process of AHN in the DG [Gould and Tanapat, 1999], while chronic positive stimulation (e.g. environmental enrichment) up-regulates the process [Olson et al., 2006]. Many anti-depressant treatments also up-regulate AHN back to pre-stress levels, on a time course that is akin to the time course that is required for the behavioral depressive symptoms to disappear [Dranovsky and Hen, 2006, Warner-Schmidt and Duman, 2006]. Increased levels of CORT play a part in this regulation of AHN [Saaltink and Vreugdenhil, 2014], although it depends on the

circumstances whether increased CORT decreases or increases AHN [Lehmann et al., 2013]. AHN in the temporal DG is more sensitive to chronic stress than AHN in the septal DG. Much more detail of the role of the mammalian hippocampus in the stress response can be found in review articles by Jacobson and Sapolsky [1991], Levone et al. [2015] and Radley [2012].

Brief overview of the avian hippocampal formation

The avian HF is homologous to the mammalian hippocampal formation [Striedter, 2016], a fact also reviewed in much more detail in other contributions to this special issue. Many subdivisions have been proposed in the avian HF. The main subdivisions, as viewed in coronal sections, are the ventral "V" area (including the lateral and medial laminae and the enclosed triangle), the dorsomedial area (DM; including a few smaller subdivisions which are distinct in their gene expression and their connectivity) and a the dorsolateral area (DL), through which most of the telencephalic inputs into the HF reach the rest of the structure (Fig. 2). This general structure is maintained along the entire rostro-caudal axis of the HF, although all structures are angled from ventromedial in rostral sections to dorsolateral in more caudal sections [Erichsen et al., 1991]. Different authors have interpreted different subdivisions as homologous with different mammalian hippocampal subfields, but this is not the topic of this review.

If the interaction with the HPA axis is an ancestral trait of the HF, then there is a good possibility that this trait has been conserved in the avian HF as well. In this review, I will explore whether the avian HF controls the HPA axis response as part of a negative feedback loop, whether it responds to stress and to glucocorticoid hormones, and whether there is a sub-regional specialization in the avian HF equivalent to that along the septo-temporal axis in the mammalian hippocampus.

HPA regulation by the avian hippocampal formation

If the avian HF plays a role in negative feedback on the HPA axis, then it needs to detect CORT levels at both baseline and induced levels. Indeed, like the mammalian hippocampus, the avian HF

126 expresses both GR and MR. And also like in mammals, MR has a more restricted expression pattern
127 across the brain, with the highest expression levels in the HF [Dickens et al., 2009, Dickens et al.,
128 2011, Hodgson et al., 2007, Krause et al., 2015, Senft et al., 2016, Shahbazi et al., 2011]. MR
129 expression levels in the HF were lower in zebra finches (*Taeniopygia guttata*) that had been
130 selectively bred for increased peak CORT levels after an acute stressor, while GR expression levels
131 did not differ between the selected line of birds and randomly bred birds [Hodgson et al., 2007].
132 Chronically stressed starlings (*Sturnus vulgaris*) also had reduced MR expression levels in the HF
133 compared to controls, again with no effect on hippocampal GR (although GR levels in the PVN in the
134 hypothalamus did differ) [Dickens et al., 2009]. This suggests active regulation of MR expression
135 based on stimulation by repeated high CORT titers, and an important role for the HF in a negative
136 feedback loop controlling CORT levels.

137 Experimental manipulation of the HF confirms its role in HPA axis regulation. In pigeons (*Columba*
138 *livia*), the hypothalamic control of the release of corticosterone, mediated by the PVN, is dependent
139 on the activity of the HF (among other areas). Hippocampal lesions lead to a loss of circadian rhythm
140 in CORT titers, with the titers staying continuously at the highest level of the normal circadian
141 rhythm [Bouillé and Baylé, 1973] (Fig. 3A). Although the baseline levels are higher, the increase in
142 CORT induced by restraint stress is actually slightly lower than in intact animals, which the authors
143 interpret as a consequence of a stronger negative feedback (or less sensitive adrenal glands) due to
144 the chronically elevated activation of the HPA axis. This suggests that the HF plays an inhibitory role
145 in the regulation of the HPA axis, just like it does in mammals. Recordings of multi-unit activity in the
146 HF confirmed this hypothesis. Generally, firing rates were high throughout the day, but there was a
147 marked drop of activity in the middle of the night, coinciding with an increase in activity in the
148 hypothalamus, and preceding the morning CORT peak by about 2-3 hours, similar to the recorded
149 lag between Corticotropin Releasing Factor (CRF) and CORT peaks in the morning [Bouillé and Baylé,
150 1976]. These studies also confirmed that HF influences the circadian CORT cycle by suppressing
151 electrophysiological activity in the hypothalamus, because lesions in the HF led to the loss of the

circadian cycle in hypothalamic activity [Bouillé and Baylé, 1978]. Electrical stimulation of the HF confirmed its inhibitory role in the control of the HPA axis: 10 minutes of stimulation led to a significant suppression of corticosterone in plasma (Fig. 3B) [Bouillé and Baylé, 1973].

The same authors investigated how the inhibitory effect of the HF on the HPA axis was mediated anatomically. Partial deafferentation of the hypothalamus suggested that the inputs that bring the inhibitory signals from the HF come from anterior and lateral [Bouillé et al., 1975]. Early investigations of connectivity, based on degenerating axons for anterograde tracing and on HRP injections for retrograde labelling, suggested a direct connection between the HF and some areas of the hypothalamus [Bons et al., 1976, Bouillé et al., 1977]. A number of tract tracing studies have followed, and confirmed that the HF in birds has direct projections to the hypothalamus [Atoji et al., 2002, Atoji and Wild, 2004, Szekely and Krebs, 1996], via what some consider the equivalent of the post-commissural fornix [Atoji and Wild, 2004]. These axons originate mostly in the lateral-most part of the DM region , although earlier retrograde tracing studies had also suggested cell bodies located in the ventral V area [Bouillé et al., 1977]. Like in mammals, it seems that there are no direct connections from the HF to the PVN itself, but there may be several indirect connections which are similar to those in mammals. Some of these connections are via other hypothalamic nuclei (e.g. lateral hypothalamus) [Atoji et al., 2002, Atoji and Wild, 2004, Casini et al., 1986, Korf, 1984, Szekely and Krebs, 1996], while others possibly involve the medial and lateral septal nuclei [Atoji et al., 2002, Atoji and Wild, 2004], the nucleus of the diagonal band [Krayniak and Siegel, 1978a, Krayniak and Siegel, 1978b] and the BNST [Atoji et al., 2006] (Fig. 1B). In mammals, the connection from the lateral septum to the PVN is known to activate, rather than inhibit the HPA axis [Cullinan et al., 2008], so a similar functional connectivity is possible in birds as well. The relative contributions of the different physical pathways to the hippocampal control of HPA activity remains to be elucidated, as is indeed the case in mammals.

Avian hippocampal response to stress

177 The levels of MR and GR expression in the avian HF suggest not only that the avian HF is involved in
178 HPA feedback regulation, but also that the avian HF could respond to stress in a similar way to the
179 mammalian hippocampus. In mammals, there are several morphological responses to chronic stress
180 in the hippocampus. As pointed out in the introduction, AHN in mammals is sensitive to levels of
181 chronic stress [Gould and Tanapat, 1999], as well as to levels of cognitive or emotional enrichment
182 [Olson et al., 2006]. In addition, in human patients suffering from major depressive disorder, as well
183 as in some non-human primates undergoing chronic stress, the volume (or the amount of grey
184 matter) of the hippocampus shrinks, especially after several depressive episodes [Czeh and
185 Lucassen, 2007, McKinnon et al., 2009, Willard et al., 2011, Willard et al., 2009]. This seems mainly
186 due to a shrinkage in dendritic arborization of CA1 pyramidal cells without a loss of neurons
187 [Lucassen et al., 2014], although an increase in apoptosis in the dentate gyrus has also been
188 detected in animal models of chronic stress [Kubera et al., 2011]. In birds as well, there is some
189 evidence that AHN and/or hippocampal volume can respond to stress.

190 Nikolakopoulou et al. [2006] investigated the effects of an acute stressor on cell proliferation in the
191 avian HF. They injected day-old chicks (*Gallus gallus domesticus*) with BrdU (Bromo-deoxy-Uridine,
192 which is incorporated in the DNA of dividing cells), and presented them with either nothing, a bead
193 coated with water, or a bead coated in methyl-anthranilate, a bitter substance. This is a procedure
194 used to study one-trial learning, as chicks that have one experience with the bitter bead will avoid
195 pecking that bead from then on [Sandi et al., 1992]. Chicks that were exposed to the bitter substance
196 had a lower numbers of $BrdU^+$ cells 24 hours after the experience, and this was mainly in the DL part
197 of the HF. They also had fewer $BrdU^+$ cells in DM, but no differences in the V. However, when they
198 checked 9 days after the exposure, these differences in the numbers of $BrdU^+$ cells that survived for
199 that long had disappeared. This suggests an effect of an acute stressor on cell proliferation in the HF,
200 combined with a homeostatic system that keeps the number (rather than the proportion) of
201 surviving new cells constant.

Other (chronic) stressors have been shown to affect longer-term survival of new neurons in the avian HF. Robertson et al. [Submitted] compared 12-week-old commercially food-restricted broiler breeder hens to hens that had had access to *ad lib* food for the last 6 weeks of that period. The food restricted birds grew more slowly, although the size of their brains and indeed hippocampal volume did not differ from the *ad lib* birds. Interestingly, the 1-week survival of $BrdU^+$ hippocampal neurons (double-labelled for Hu, a neuronal marker) did differ, with fewer of them in the food restricted birds. A similar pattern was found for $BrdU^+$ non-neuronal cells, but not for the population of $BrdU^+$ cells in the ventricular zone. This suggests that with this type of chronic stressor (the chickens were shown to be chronically hungry; [Dunn et al., 2013]), it is the survival (at least to 1 week) of new hippocampal neurons that is downregulated, rather than the division of the precursor cells. This is also similar to the effect of food restriction in young rats [Cardoso et al., 2016].

Another possible chronic stressor is captivity, at least for wild-caught birds. Several studies have shown that small songbirds (dark-eyed juncos (*Junco hyemalis*), mountain chickadees (*Poecile gambelli*), black-capped chickadees (*P. atricapillus*), and brown-headed cowbirds (*Molothrus ater*)) that have been held in captivity for several weeks have a smaller HF, relative to total brain size than individuals whose brains were collected right after capture from the field [Day et al., 2008, LaDage et al., 2009, Smulders et al., 2000a, Tarr et al., 2009]. Using different methods, both Ladage et al. [2010] using doublecortin (DCX) as a marker of AHN [Boseret et al., 2007, Brown et al., 2003, Francis et al., 1999] in mountain chickadees singly-housed indoors, and Barnea and Nottebohm [1994], using ^{3}H-Thymidine to label new neurons in black-capped chickadees group-housed out-doors, found reduced AHN in birds that had been kept in captivity for 6 weeks or more. Surprisingly, Tarr et al. [2009] did not find significant differences in AHN between captive (singly-housed, indoor) and wild birds. It is possible that BrdU is less sensitive, and that a larger population of new neurons is identifiable with the radioactive method or with DCX. Dividing stem cells and precursor cells that are labeled will continue to feed labeled daughter cells into the brain with each subsequent cell division. Because the label is diluted by a factor of 2 with each division, it is possible that the silver grain auto-

radiography method used with ^{3}H-Thymidine is more sensitive in picking up such cells than the colorimetric antibody staining used for BrdU. DCX staining identifies all new neurons, at different stages of maturation.

One of the main problems with interpreting captivity studies, is that the effect of captivity on the HF may be due to different factors: it could indeed be an effect of chronic stress, but captivity also severely limits the complexity of the animals' cognitive experiences. And in mammals, at least, environmental complexity is a factor that affects hippocampal volume (and that of other brain areas as well) and AHN [van Praag et al., 2000]. There is, however, one set of studies that allows us to at least speculatively separate these two aspects of captivity: the study of Pravosudov and colleagues' hand-reared black-capped chickadees. One could argue that birds that have been hand reared in a lab environment would not experience that environment as nearly as stressful as wild-caught birds would. However, the complexity of the environment would still be much lower in the lab than in the field, even for hand-reared animals. Comparing hand-reared to wild-caught captive birds and to birds whose brains were collected directly from the wild, they found that hand-reared birds, like captive wild-caught birds, had a smaller hippocampal volume than wild birds. However, unlike the captive wild-caught birds [Ladage et al., 2010], they had the same number of DCX+ hippocampal cells as wild birds [Roth et al., 2012]. This suggests that AHN in the avian hippocampus is indeed sensitive to chronic stress.

Housing conditions can also lead to social stress. Social isolation is very likely to be a stressful event for social animals, and singly-housed zebra finches have lower neurogenesis in the hippocampal formation than group-housed birds [Barnea et al., 2006]. Subordinate mountain chickadees are expected to be subject to chronic stress due to their social status, especially when housed in relatively small enclosures, and levels of cell proliferation (measured 2 days after BrdU injection) in the hippocampal ventricular zone are indeed lower in the subordinate than in the dominant birds [Pravosudov and Omanska, 2005a].

253 This does not mean that AHN only responds to stress, and not to more subtle differences in cognitive
254 stimulation. Mountain chickadees that are allowed to hoard and retrieve have more DCX+ cells in
255 the HF than birds that are not given that opportunity [LaDage et al., 2009]. Similarly, domesticated
256 pigeons housed singly for 6 weeks in bare cages had fewer DCX+ neurons in the ventral HF than
257 those held in enriched cages (objects and toys) of slightly larger size [Melleu et al., 2016]. This effect
258 was specific to hippocampal neurogenesis, as neurogenesis in the medial striatum did not respond at
259 all, while that in lateral striatum was actually higher in the bare cages. Surprisingly, in this particular
260 study, the animals housed in enriched cages had longer tonic immobility scores and spent more time
261 immobile when presented with novel objects and novel environments than the bare-cage animals.
262 This would suggest that they are more anxious than the birds from bare cages. Anxiety typically goes
263 together with the experience of chronic stress. It is possible that the stress responsivity was blunted
264 by chronic stress response activation in the birds from bare cages, leaving the enriched animals with
265 the stronger response; or indeed, the contrast between home cage and test environment may have
266 been larger for the enriched animals [Melleu et al., 2016].

267 Since the HF has very high levels of MR and GR, it is logical to ask whether CORT levels are
268 responsible for the changes in AHN in response to stressors. Even though subordinate chickadees
269 have fewer $BrdU^+$ neurons than dominant ones [Pravosudov and Omanska, 2005a], CORT levels do
270 not differ from the dominant birds [Pravosudov et al., 2003]. Consistent with this apparent
271 disconnect, direct manipulation of CORT at intermediate, physiological levels for 49 days in the same
272 species does not affect hippocampal cell proliferation as measured two days after BrdU injection
273 [Pravosudov and Omanska, 2005b]. Similarly, 28 days of increased CORT titers using silastic implants
274 did not change hippocampal neurogenesis (measured 24 days after BrdU injections) in song
275 sparrows (*Melospiza melodia*) [Newman et al., 2010]. However, in this study, there was an
276 interaction between CORT and dihydroepiandrosterone (DHEA). Systemic DHEA treatment over the
277 same period increased hippocampal cell proliferation (but not maturation or migration [Wada et al.,
278 2014]), and CORT treatment counteracted that effect when the two were combined [Newman et al.,

279 2010]. DHEA is often released during the stress response, and is believed to have opposite effects to
280 those of CORT. The levels of DHEA and CORT in different brain areas (including the HF) respond
281 differently from each other to seasonal changes and to acute stressors, and they respond differently
282 than hormone titers measured in plasma, making this finding complicated to interpret [Newman and
283 Soma, 2009]. Even though in vivo manipulations of chronic CORT levels does not seem to affect
284 hippocampal neurogenesis in birds, it has been shown *in vitro* that CORT can reduce cell
285 proliferation in the ventricular zone by binding to glucocorticoid receptors (GR), at least in male
286 zebra finches (but not in females) [Katz et al., 2008]. It is clear therefore that CORT may well play a
287 role in the stress regulation of hippocampal neurogenesis, but it is by no means a straightforward
288 role. Whether it follows the same complicated patterns as in mammals remains to be determined.

289 **Is there a sub-regional specialization in the avian hippocampal formation?**

290 As indicated in the introduction, it is the temporal pole of the mammalian hippocampus which is
291 most sensitive to chronic stress and which is involved in regulating the HPA axis' response to stress,
292 while the septal pole of the hippocampus may play a greater role in cognitive information processing
293 [Fanselow and Dong, 2010], and potentially the regulation of the circadian CORT cycle [Herman and
294 Mueller, 2006]. It is possible, therefore, that the avian HF has a similar regional subdivision (or at
295 least gradient) with cognitive function on one end, and more emotion-related functions on the other
296 end. Given that the relevant axis in mammals is perpendicular to the axis along which the better
297 known subdivisions of the HF (dentate gyrus, Ammon's horn, subiculum) are organized, and starts
298 from the physical connection to the septum on one end, I will explore the same axis in birds. In the
299 avian HF, the rostral pole is physically connected to the septum, and as you move rostral to caudal,
300 the same general subdivisions can be found in coronal sections all along the HF (see earlier; Fig. 2).
301 In reality the axis is probably slightly more rostromedial to caudo-lateral [Herold et al., 2014], so
302 running at an angle away from the midline, moving from the septal pole in the front to the
303 "temporal" pole at the back. The hypothesis being explored, therefore, is that a rostro-caudal axis

304 exists in birds, which is equivalent to the septo-temporal axis in mammals. Few researchers have
305 explicitly explored the rostro-caudal axis in the avian HF, so not much evidence is available to test
306 this hypothesis. Nevertheless, there are a number of studies that have information on this axis. Most
307 of these studies did not subdivide the HF into the subdivisions that are visible in coronal sections, so
308 there is a possibility that rostro-caudal differences are confounded with subdivisional differences in
309 some of these studies.

310 Atoji and colleagues specifically investigated differences in connectivity along the rostro-caudal axis
311 of the HF [Atoji et al., 2002, Atoji and Wild, 2004]. Their conclusion was that generally speaking,
312 most of the external connections (both efferent and afferent) of the HF did not differ along the
313 rostro-caudal axis, as long as you took account of the fact that the entire structure sits progressively
314 more laterally as you go further caudal along the brain. Nevertheless, there are some patterns that
315 clearly point to a rostro-caudal specialization. The projections from the HF to the septal nuclei are
316 topographically organized, with caudal HF projecting to the post-commissural septum, and more
317 rostral areas projecting to the nucleus of the diagonal band and the rostral septum [Atoji et al., 2002,
318 Atoji and Wild, 2004, Krayniak and Siegel, 1978a, Krayniak and Siegel, 1978b, Montagnese et al.,
319 2008]. Projections to the contralateral HF are also topographical, with rostral connecting to rostral
320 and caudal to caudal [Atoji et al., 2002, Atoji and Wild, 2004]. Input from nucleus Taeniae of the
321 amygdala (TnA) is limited to the middle third of the HF, with some input to the caudal third, but
322 none to the rostral third [Atoji et al., 2002]. There was also a suggestion in Krayniak and Siegel
323 [1978a]'s study that only the caudal HF might project to the amygdala-like areas in the Arcopallium
324 and TnA, but later work suggests that this may be more widespread [Atoji et al., 2002]. However, the
325 path of the axons does differ along the rostro-caudal axis, with caudal HF sending axons
326 dorsolaterally around the lateral ventricle, while the rostral axons run ventromedially [Atoji et al.,
327 2002]. The projections to the BNST, which in mammals are restricted to the temporal subiculum,
328 originate all along the rostrocaudal axis in the avian HF, suggesting a clear subiculum-like cell
329 population around the boundary between the DM and DL area, but no rostro-caudal specialization in

this connection [Atoji et al., 2006]. Whether a more subtle topographical organization exists in de BNST itself remains to be investigated.

The expression of most genes and neurotransmitters seem to delineate the different "coronal" subdivisions of the HF, along the entire extent of the rostro-caudal axis. Nevertheless, there are a few that show a rostro-caudal gradient that might hint at a functional specialization. NMDA receptor expression is more distinct among the different subdivisions in caudal than in rostral HF, indicating some areas have higher NMDA-binding capacity in the rostral, compared to the caudal HF. $5HT_{1A}$ receptor labelling was also lower in the caudal compared to the rostral HF [Herold et al., 2014], which the authors relate to lower 5-HT levels detected in the caudal HF of pigeons in a previous study [Krebs et al., 1991]. The latter is in contrast to the mammalian pattern, which shows more 5-HT innervation in the temporal than the septal pole of the hippocampus [Bjarkam et al., 2003, Gage and Thompson, 1980], and might argue against our hypothesis that the caudal HF is more involved in emotional processing. Finally, choline acetyltransferase staining is denser in the caudal DL than in the more rostral sections [Krebs et al., 1991], implying heavier cholinergic innervation of the caudal HF. This does match the pattern along the septo-temporal axis in rodents [Hörtnagl et al., 1991].

Several authors have counted cells at different levels along the rostro-caudal axis of the avian HF. Wild (i.e. not captively held) black-capped chickadees have a higher density of neurons in the caudal HF, compared to the more rostral locations, but seasonally, the rostral third of the HF (but not the middle or the caudal third) increases its neuron density in August, before the start of the hoarding season, and before the seasonal increase in volume of the HF [Smulders et al., 2000b]. This fits direct investigations of neurogenesis, as the number of newly-generated neurons is higher (but with shorter turn-over) in the rostral pole, and lower (but with longer turnover) in the caudal pole, especially in the autumn, when food-hoarding activity is highest in the field [Barnea and Nottebohm, 1994]. A similar pattern was found in ventricular zone cell proliferation in hand-reared marsh tits (*Poecile palustris*) during the first few months of life [Patel et al., 1997]. Keeping wild-caught

chickadees in captivity for 6 weeks (or even one week [Hoshooley et al., 2007]) in the autumn removes this rostro-caudal pattern in neurogenesis, with the largest decrease in the rostral pole and the smallest decrease in the caudal pole [Barnea and Nottebohm, 1994]. Similarly, the volume reduction following captivity in black-capped chickadees is more noticeable in the rostral 2/3 of the HF than in the caudal 1/3 [Tarr et al., 2009]. More neurons are also activated (as measured by the expression of the IEG ZENK) in the rostral HF (regions DM and DL) than in the caudal HF in this same species, in response to flying around a room and foraging, hoarding and/or retrieving [Smulders and DeVoogd, 2000]. All of these findings hint at a possible role of the rostral HF in cognitive function, which is in high demand in the field at this time of year, but not in captivity. However, other species, in different conditions, have different rostro-caudal patterns of neurogenesis. In zebra finches, more new neurons can be found in the caudal than in the rostral parts of the HF [Barnea et al., 2006]; and in brown-headed cowbirds and red-winged blackbirds (*Agelaius phoeniceus*) the caudal ventral HF also has a higher density of DCX staining and more DCX+ round and fusiform cells, although the effect is not there in area DM (analysis of the supplementary raw data of Guigueno et al. [2016]). The reason for these species differences remain to be investigated.

The most convincing evidence for a rostro-caudal functional specialization would come from selective activation or inactivation studies. However, these are few and far between. Most lesion experiments destroy the HF along its entire rostro-caudal extent. There is one exception: Bouillé and Baylé [1973] found that hippocampal lesions (aimed at the V area) including a rostral and a caudal site doubled the increase in CORT titers between 8 and 10 AM compared to a caudal lesion alone (Fig. 3C). Stimulation of the ventral HF, however, resulted in a much stronger suppression of CORT titers when performed in the caudal-most site in the experiment (A 5.0 in Karten and Hodos [1967]) than when stimulation happened at more rostral sites (A 5.5 - A7.0) [Bouillé and Baylé, 1973] (Fig. 3B). This at least hints at the possibility that the caudal HF plays a stronger role in the suppression of the HPA axis than the rostral HF.

Conclusion

The evidence is clear that the avian HF, like the mammalian hippocampus, plays a role in the control of the HPA axis and responds strongly to stressful conditions. What is less clear, however, is whether there is a regional specialization in the avian HF akin to the septo-temporal axis specialization in the mammalian hippocampus. Whereas some evidence is consistent with the idea that the rostro-caudal hippocampal axis may be the avian equivalent (stronger HPA suppression with caudal stimulation, gradient of extrinsic cholinergic innervation), other evidence contradicts this idea (reversed gradient of extrinsic 5-HT innervation, lack of rostro-caudal pattern in the projection to the BNST). Like with other subdivisions of the avian HF, it is likely that both modern avian and mammalian organizations at least partially evolved after the split from the last common ancestor, and that there are therefore both similarities and differences in how the hippocampal formations interact with stress and the HPA axis.

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Figure captions

Figure 1. The hippocampus in both birds and mammals is known to influence the activity of the HPA axis. In this figure, known connectivity patterns between the hippocampus and the paraventricular nucleus of the hypothalamus in both groups are summarized. A. Summary diagram of the

404 connectivity between the hippocampus and the hypothalamic paraventricular nucleus (PVN) in
405 mammals. Arrows with "+" next to them represent excitatory connections, and arrows with "-" next
406 to them represent inhibitory connections. This diagram is adapted from Figure 3 in Herman and
407 Mueller [2006], with addition of data from [Cullinan et al., 2008]. B. Summary diagram of some of
408 the potential pathways between the avian hippocampal formation (HF) and the avian PVN. The
409 connectivity in this diagram is drawn together from Atoji et al. [2002], Atoji et al. [2006], Atoji and
410 Wild [2004], Casini et al. [1986], Korf [1984], Krayniak and Siegel [1978a], Krayniak and Siegel
411 [1978b], and Szekely and Krebs [1996]. The diagram by no means comprehensively summarizes all
412 the studies looking at connectivity between the nuclei listed. Abbreviations: BNST: Bed Nucleus of
413 the Stria Terminalis, LHy: Lateral Hypothalamus, MH: medial hypothalamus, NDB: Nucleus of the
414 Diagonal Band, peri-PVN: area around the PVN, sub-VPN: area ventral to the PVN, vlDMH:
415 ventrolateral Dorsomedial Hypothalamus, vlPOA: ventrolateral Preoptic Area.

416

417 **Figure 2.** "Coronal" subdivisions in the avian hippocampal formation in a pigeon at different rostro-
418 caudal levels anterior of the zero-point indicated in Karten and Hodos [1967]. Figure adapted with
419 permission from Figure 2 in Herold et al. [2014]. The three main subdivisions are the ventral (V),
420 dorsomedial (DM) and dorsolateral (DL) areas, each with their further subdivisions (Vl: lateral branch
421 of the V-shaped layer; Vm: medial branch of the V-shaped layer, Tr: triangular area between the two
422 branches of the V-shaped layer; DMv: ventral part of DM; DMd: dorsal part of DM; DLv: ventral part
423 of DL; DLd: dorsal part of DL).

424

425 **Figure 3**: Effects of hippocampal lesions and stimulation on CORT plasma titers in pigeons. Data
426 taken from the tables by Bouillé and Baylé [1973]. **A**. Change in circadian CORT titer rhythms as the
427 result of lesions placed in both rostral (A7.0) and caudal (A5.5) location in the HF (white symbols),
428 compared to the circadian CORT rhythm in the same birds before lesion (black symbols). Data are

from 4 birds. **B**. Effects of 10 minutes of electrical stimulation at 4 different rostro-caudal locations in the pigeon HF on CORT titers. Stimulation was always performed between 8 and 10am. Sample sizes are indicated in the figure. Error bars in all figures are suspected to be standard error of the mean, although this was not specified in the original paper. **C**. Increase in CORT titers between 8 and 10am as a result of a caudal lesion (at A5.5 according to Karten and Hodos [1967]; black symbols) and as a result of a lesion placed in a rostral (A7.0) as well as a caudal (A5.5) location; white symbols). Data are from 18 birds in each lesion group.

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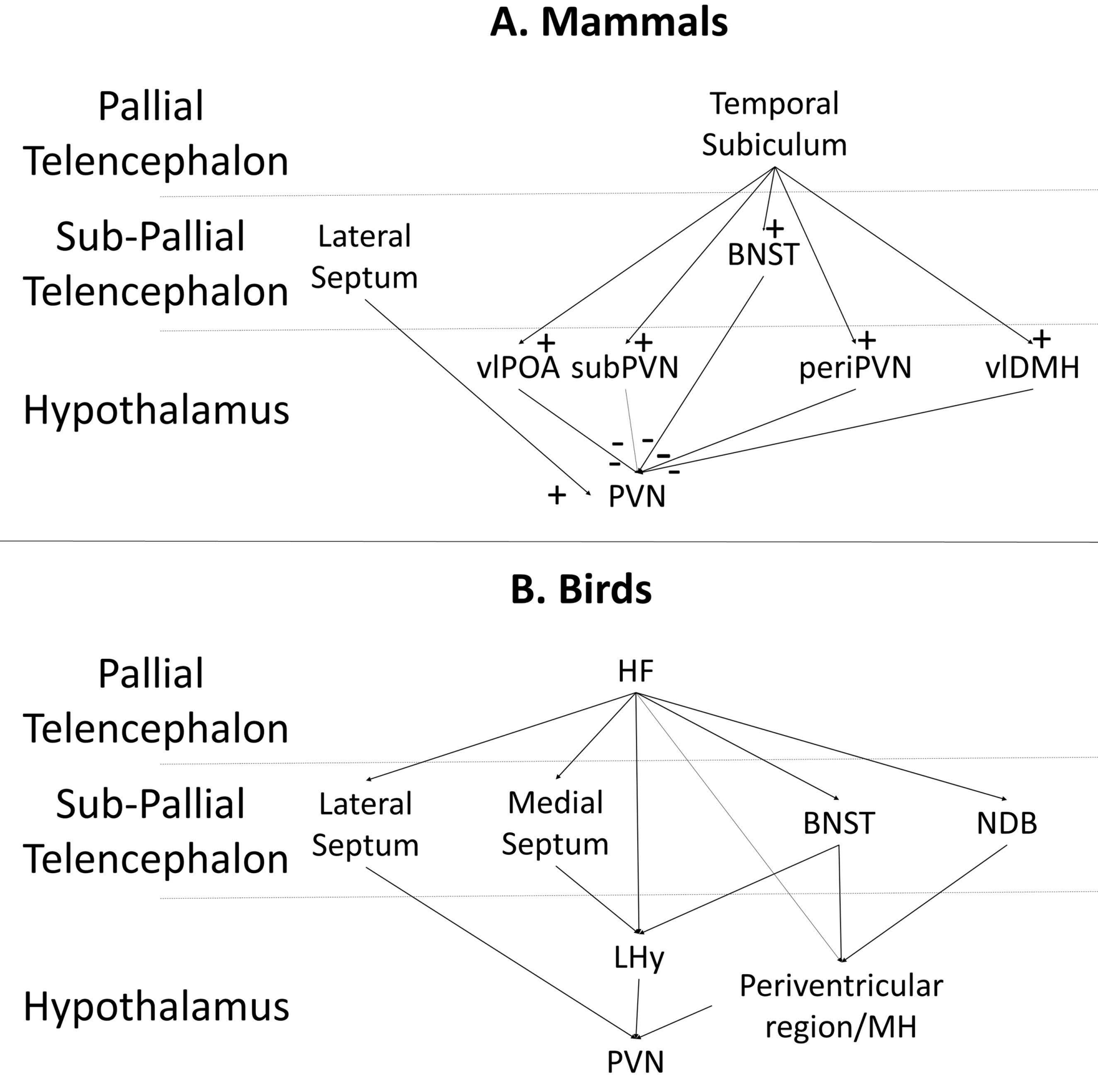
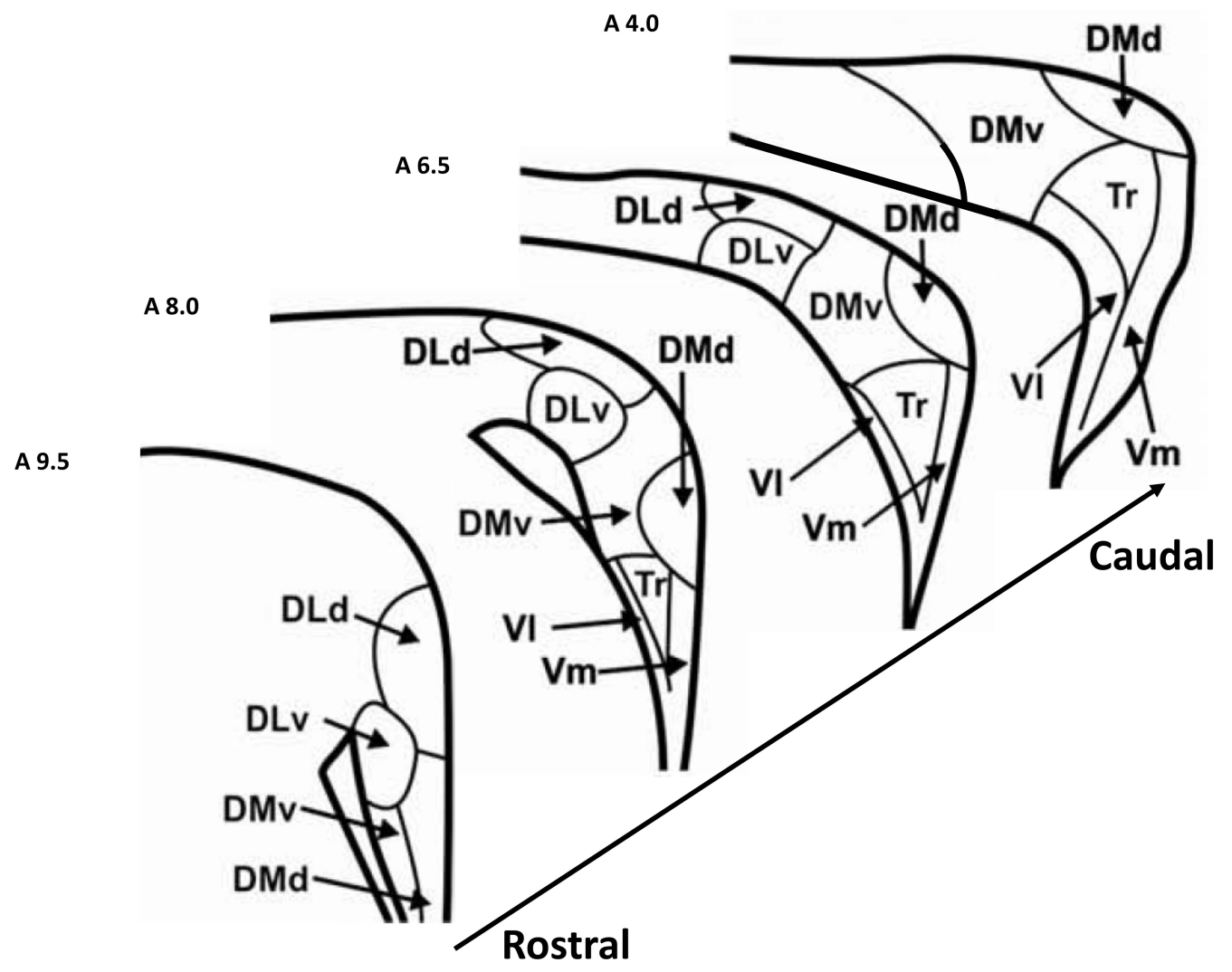

A. Mammals
Pallial Telencephalon
Sub-Pallial Telencephalon
Hypothalamus
Temporal Subiculum
Lateral Septum
BNST
vlPOA
subPVN
periPVN
vlDMH
PVN
B. Birds
Pallial Telencephalon
Sub-Pallial Telencephalon
Hypothalamus
HF
Lateral Septum
Medial Septum
BNST
NDB
LHy
Periventricular region/MH
PVN


A 4.0
DMd
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A 8.0
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A 9.5
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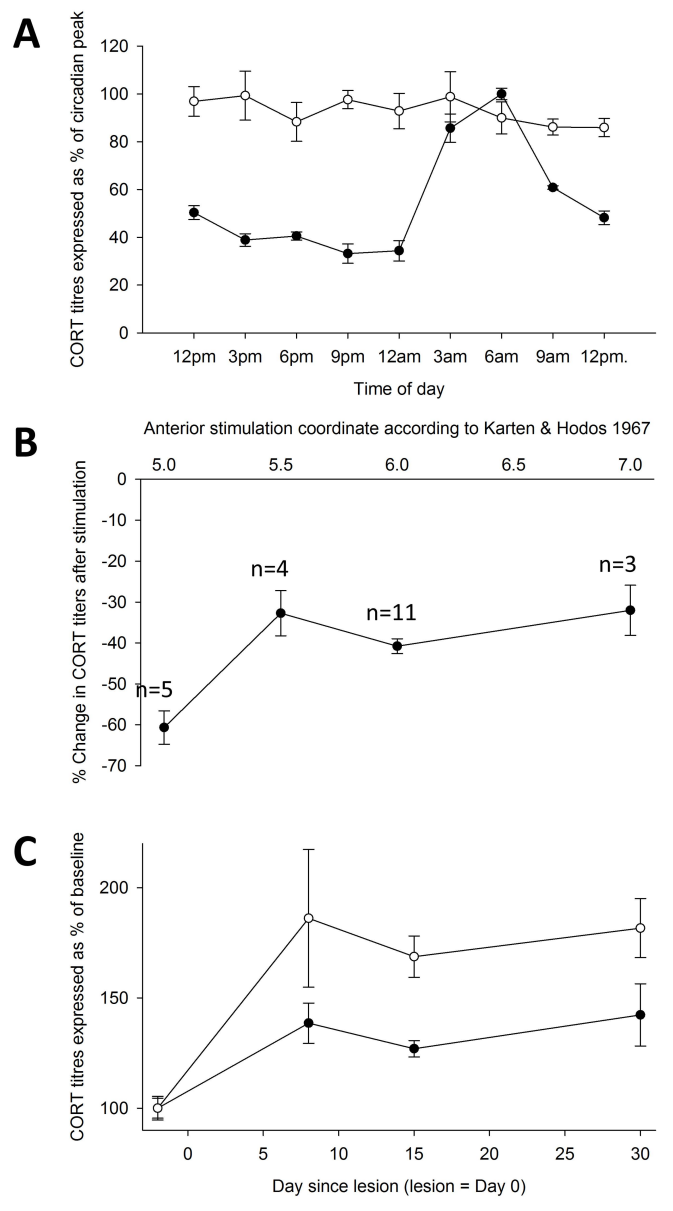
DMd
Caudal
Rostral


A
CORT titres expressed as % of circadian peak
120
100
80
60
40
20
0
12pm 3pm 6pm 9pm 12am 3am 6am 9am 12pm.
Time of day
B
Anterior stimulation coordinate according to Karten & Hodos 1967
5.0 5.5 6.0 6.5 7.0
% Change in CORT titers after stimulation
0
-10
-20
-30
-40
-50
-60
-70
n=5
n=4
n=11
n=3
C
CORT titres expressed as % of baseline
200
150
100
0 5 10 15 20 25 30
Day since lesion (lesion = Day 0)